Antihypertensive therapy with aliskiren

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Aliskiren represents the first member in a new class of antihypertensive drugs. Inhibiting the renin–angiotensin system at its rate-limiting step is an idea that has been pursued for >30 years; however, earlier compounds failed because of problems related to efficacy, bioavailability, and/or side effects. Aliskiren, a 610 Da nonpeptide molecule, has exceptional affinity for the human renin enzymatic site and a half-life of about 40 h, which make its 3% bioavailability clinically unimportant with continued administration. The drug is not metabolized by CYP P450 enzymes and is excreted >90% unchanged by the fecal route. No adjustments are necessary for renal function, liver function, age, ethnicity, or other prescribed drugs. Blood pressure reductions are similar to those provided by other monotherapies. Interestingly, aliskiren combined with angiotensin receptor blocker or angiotensin-converting enzyme inhibitor therapy leads to a further blood pressure reduction as does combination with a diuretic or calcium channel blocker. The fact that plasma renin activity is reduced to low levels with aliskiren could provide a theoretical advantage over other treatments, while increases in total renin (prorenin) after the drug poses additional food for thought. Studies with primary cardiovascular and renal end points to address these possibilities are in progress.

Kidney International (2008) **73,** 679–683; doi:10.1038/sj.ki.5002732; published online 26 December 2007

KEYWORDS: angiotensin; blood pressure; cardiovascular disease; hypertension; renin–angiotensin system

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Received 28 July 2007; revised 9 October 2007; accepted 10 November 2007; published online 26 December 2007

PHARMACOLOGY

Excellent comprehensive reviews on oral renin inhibitors have been published recently.[1] The readership is well familiar with the renin–angiotensin system, the functional cascade, and notions on peptides and enzymes beyond angiotensin (Ang) II that are discussed in detail elsewhere.[2] Aliskiren, (2(S),4(S),5(S),7(S)-*N*-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy)phenyl]-octanamide hemifumarate), or $C_{30}H_{53}N_3O_6$ (Figure 1), is a nonpeptide direct renin inhibitor.[3] The molecule occupies specific subsites within the enzymatic pocket of the renin molecule, thereby blocking the function of the enzyme. Aliskiren is a hydrophilic molecule with high aqueous solubility. Aliskiren exhibits a high specificity for human renin over other human aspartic peptidases (10 000-fold lower affinity) or non-human renins. For instance, the IC_{50} values for human renin (0.6) are superior compared to those for marmoset renin (2), rat renin (80), pig renin (159), or cat renin (8500); these findings underscore the drug's species specificity. The species specificity also explains why aliskiren was first investigated in the marmoset, a most difficult animal model, and subsequently in transgenic rats outfitted with the human renin and human angiotensinogen transgenes.[4–6]

Renin is released as an active enzyme by the kidney and as prorenin by other tissues, including the eye, testis, ovary, adrenal gland, salivary gland, and mast cells.[7] Prorenin features a 43 amino-acid N-terminal handle region that covers the enzymatic site. A prorenin/renin receptor has been cloned that is expressed by numerous cell types. When prorenin occupies this receptor, the molecule is activated through an opening of the handle region and is then capable of cleaving angiotensinogen. Aside from activating prorenin, the renin receptor also signals via the ERK1/2 (extracellularly regulated kinase) pathway (Figure 2). The prorenin/renin receptor and its signaling is an extremely interesting area of research and is reviewed elsewhere.[8] Aliskiren blocks the enzymatically active site of renin. There is no evidence that aliskiren blocks the prorenin/renin receptor or its signaling pathway (DN Müller, personal communications, 2007). However, when prorenin is activated by docking to the receptor, aliskiren can, of course, occupy the enzymatic pocket and block the activated renin.

In patients and animal models treated with aliskiren, plasma renin activity (PRA), namely the amount of Ang I

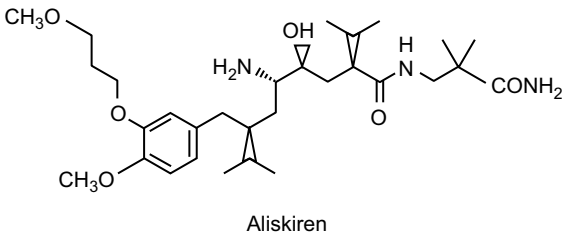

Figure 1 | Chemical structure of aliskiren is shown.

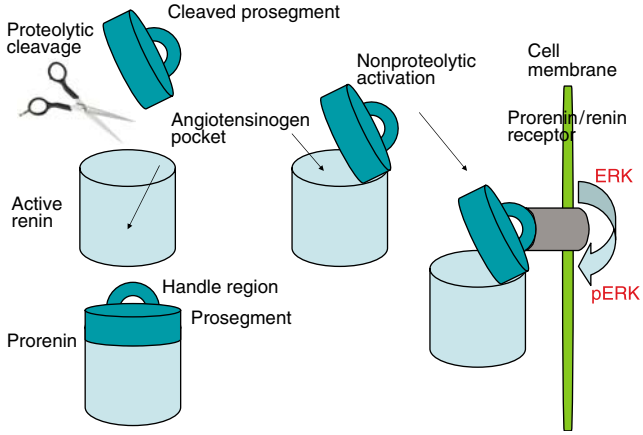

Figure 2 | Prorenin features a handle region that blocks the enzymatic pocket. Active renin is released from the kidney, without the prosegment. Otherwise, prorenin is released from other sites that can be activated proteolytically (freezing or acid treatment) or nonproteolytically by binding to the prorenin/renin receptor. When bound to the receptor, the handle region opens and renin can locally cleave angiotensinogen. The renin receptor also signals via ERK1/2.

generated per h, is reduced to low values. Ang II concentrations are also reduced and aldosterone concentrations are significantly decreased. However, total renin, which can now be measured by an immunoradiometric assay, is increased. Kang *et al.*[9] have published dramatic multiphoton fluorescence micrographs of afferent arterioles of animals receiving angiotensin-converting enzyme (ACE) inhibition, AT1 receptor blockade (ARB), or aliskiren. ACE inhibitors and ARB increase PRA, whereas aliskiren reduces PRA at the afferent arteriole. The significance of increased total renin, or reduced PRA, after aliskiren treatment is not entirely clarified. Sealey and Laragh[10] have hypothesized that the increase in total renin might pose some cardiovascular risk (see below). Menard and Azizi[11] have argued against that possibility.

Aliskiren exhibits interesting kinetics.[12–19] The drug half-life is about 40 h. Thus, a plateau is reached after about a week's ingestion to concentrations of about 350 ng ml^{-1}. The half-life is not influenced by renal function or liver function, even though the biliary tract is the principle mode of elimination. No effect of ethnicity was shown when Japanese and Caucasian subjects were compared. Aliskiren kinetics were measured in the presence of various other drugs, including irbesartan, lovastatin, atenolol, celecoxib, furosemide, and cimetidine; no interactions were demonstrated with the exception that irbesartan reduced the C_{max} of aliskeren by 50% and aliskeren reduced the area under the curve (AUC) and C_{max} of furosemide. When aliskeren was administered with a high-fat meal, both the AUC (70%) and C_{max} (85%) of aliskeren were reduced. Aliskiren is not metabolized by CYP P450 enzymes and is only slightly methylated and hydroxylated. The vast bulk of ingested drug is eliminated in the stool, as the bioavailability of the drug is only about 3%. Aliskiren is extremely well tolerated and the side effect profile has equaled placebo in all trials reported to date.

PROOF OF THE PUDDING

That is all very nice, but how well does aliskiren lower blood pressure (BP)? Gradman *et al.*[20] performed a randomized, multicenter, double-blind, placebo-controlled, active-comparator, eight-week trial in patients with mild-to-moderate hypertension, in which 652 patients were randomized to receive double-blind treatment with once daily oral doses of aliskiren (150, 300, or 600 mg), irbesartan 150 mg, or placebo. Aliskiren 150, 300, and 600 mg effectively lowered both trough mean sitting diastolic BP (DBP) and systolic BP (SBP). For trough DBP, the values were 9.3, 11.8, and 11.5 mm Hg, respectively, vs 6.3 mm Hg for placebo. Reductions in trough SBP were 11.4, 15.8, and 15.7 mm Hg, respectively, vs 5.3 mm Hg for placebo. The antihypertensive effect of aliskiren 150 mg was similar to that of irbesartan 150 mg. Aliskiren 300 and 600 mg lowered mean sitting DBP significantly more than irbesartan 150 mg. The emphasis on DBP was not the manufacturer's idea. Instead, DBP still receives much attention in all clinical trials, as the importance of SBP, compared to DBP, has not yet filtered down to the Food and Drug Administration requirements for demonstration of antihypertensive efficacy.

Oh *et al.*[21] studied patients with mean sitting DBP 95–109 mm Hg. They were randomized to aliskiren 150, 300, or 600 mg or placebo once daily for 8 weeks. The patients then entered a 2-week, treatment-free, withdrawal period. In total, 672 patients were randomized to treatment. After 8 weeks, aliskiren 150, 300, and 600 mg reduced mean sitting SBP/DBP by 13.0/10.3, 14.7/11.1, and 15.8/12.5 mm Hg, respectively, vs 3.8/4.9 mm Hg for placebo. The BP-lowering effect of aliskiren persisted for up to 2 weeks after treatment withdrawal. This study is of interest because of the continuous observation after treatment withdrawal. The results would suggest that the concerns expressed by Sealey and Laragh[10] are unfounded.

Kushiro *et al.*[22] randomized 455 Japanese men and women with a mean sitting DBP of 95–110 mm Hg to aliskiren 75, 150, or 300 mg or placebo. The placebo-corrected reductions in mean sitting SBP/DBP were 5.7/4.0, 5.9/4.5, and 11.2/7.5 mm Hg in the aliskiren 75, 150, and 300 mg groups, respectively. Weir *et al.*[23] have recently summarized the observations in multiple clinical trials with aliskeren by pooling the study observations. Among more than 7000 uncomplicated hypertensive subjects, they found that the

antihypertensive efficacy of aliskeren was independent of age, race, or sex.[23] Jordan *et al.*[24] studied obese patients with hypertension (BMI (body mass index) $\geqslant 30\,kg\,m^{-2}$) who had not responded to 4 weeks of treatment with hydrochlorothiazide (HCTZ) 25 mg. A total of 560 patients received single-blind HCTZ (25 mg) for 4 weeks; 489 nonresponders were then randomly assigned to double-blind aliskiren (150 mg), irbesartan (150 mg), amlodipine (5 mg), or placebo for 4 weeks added to HCTZ (25 mg), followed by 8 weeks on double the initial doses of aliskiren, irbesartan, or amlodipine. After 8 weeks of double-blind treatment (4 weeks on the higher dose), aliskiren/HCTZ lowered SBP/DBP by 15.8/11.9 mm Hg, compared to placebo/HCTZ (8.6/7.9 mm Hg). However, irbesartan/HCTZ and amlodipine/HCTZ led to similar reductions (15.4/11.3 and 13.6/10.3 mm Hg, respectively). Adverse event rates were highest with amlodipine/HCTZ because of a higher incidence of peripheral edema (11.1 vs 0.8–1.6% in other groups). Thus, aliskiren provides reliable SBP/DBP reductions in various patient groups, including the obese hypertensive patient.

Villamil *et al.*[25] randomized 2776 patients to receive aliskiren (75, 150, or 300 mg), HCTZ (6.25, 12.5, or 25 mg), the combination of aliskiren and HCTZ, or placebo, in a factorial design. The primary end point was the change in SBP/DBP from baseline to week 8. PRA was assessed at these time points. Aliskiren soundly beat placebo. Combination treatment was superior to both component monotherapies in reducing SBP/DBP 21.2/14.3 mm Hg from baseline. Aliskiren/HCTZ 300/25 mg resulted in more responders and better control rates than either monotherapy. PRA was reduced by 65–72% from basal values.

Oparil *et al.*[26] randomized 1797 hypertensive patients with DBP 95–109 mm Hg and 8-h daytime ambulatory DBP ($\geqslant 90$ mm Hg) to aliskiren 150 mg ($n = 437$), valsartan 160 mg (455), a combination of aliskiren 150 mg and valsartan 160 mg (446), or placebo (459) for 4 weeks, followed by forced titration to double the dose to the maximum recommended dose for another 4 weeks. At week 8 end point, the combination of aliskiren 300 mg and valsartan 320 mg lowered mean sitting DBP from baseline by 12.2 mm Hg, more than either monotherapy (aliskiren 300 mg, 9.0 mm Hg decrease; valsartan 320 mg, 9.7 mm Hg decrease) or with placebo (4.1 mm Hg decrease). Adverse events and laboratory abnormalities were similar in all groups. The authors also focused on total renin, which increased with both drugs but more so with aliskiren; PRA, which decreased with aliskiren but increased with valsartan; and aldosterone, which decreased with valsartan and with the combination. Thus, the combination of aliskiren and valsartan at maximum recommended doses lowered BP further in patients with hypertension, with a tolerability profile similar to that with either drug alone. Other trials have demonstrated greater BP reduction with the combination of aliskeren plus amlodipine and aliskeren plus ramipril compared to monotherapy, thus extending the drug combinations that have been studied.[23]

What are the adverse effects that have emerged from these trials with this novel antihypertensive agent? From the pooled analysis of studies reported to date, the evidence indicates a reported side effect profile no different than placebo.[23] Headaches were reported less frequently with aliskeren than with placebo.[23] On the other hand, a dose-dependent incidence of diarrhea was observed with aliskeren, particularly at the 300 and 600 $mg\,day^{-1}$ doses.[23]

These are the major studies published to date (August 2007) on the efficacy of aliskiren. In all fairness, substantially more clinical data have been presented at scientific meetings and published in abstract form. Information on proteinuria reduction in diabetic patients is also available; aliskiren reduces proteinuria. What can we deduce from the information at hand? Aliskiren as monotherapy reduces SBP/DBP as well as any other antihypertensive drug as monotherapy. The kinetics are foolproof; doing harm with aliskiren, other than women contemplating pregnancy of course, appears to be difficult. Aliskiren is efficacious in a broad range of hypertensive subjects. Aliskiren works well in combination with HCTZ. Aliskiren and valsartan at maximum package insert doses when combined lower BP further. Other efficacious combination therapy with aliskeren includes amlodipine and ramipril. Aliskiren reduces circulating Ang I, Ang II, aldosterone, and PRA. Aliskiren increases circulating total renin concentration. Longer trials addressing issues of target organ damage and degree of proteinuria reduction are running or are nearing completion. These exciting findings should be tempered with the realization that the studies conducted so far have been relatively short term and do not include any information regarding outcomes.

WHO NEEDS IT?

The same question was asked when ARBs were introduced, as ACE inhibitors dominated the scene. Some purists still insist that ARBs are indicated solely for coughing patients; however, prospective randomized trials and the placebo-similar side effect profiles have convinced most clinicians that ARBs are useful. Direct renin inhibitors need to be tested. They lower Ang II and aldosterone concentrations. Whether 'escape' is possible remains to be seen. Although cathepsins have been implicated in Ang II generation *in vitro*, a relevant *in vivo* role has not been shown to our knowledge.[27] The same can be said for tonin.[28] When aliskiren was given 'on top' of valsartan or an ACE inhibitor, a further decrease in BP was observed.[23,26] Conceivably, this additional renin–angiotensin system blockade would not have occurred had the ARB or ACE inhibitor dosage been higher in these patients. However, an additional avenue of blockade remains possible. Alderman *et al.*[29] have implicated PRA as an independent risk factor, probably because PRA reflects Ang II levels. However, their population had not been treated. What high PRA levels mean in treated hypertensive patients is unclear—probably not much. The tolerability of aliskiren has been superb in the trials; the pharmacokinetics and lack of drug interactions are extremely attractive. However, aliskiren

would be expected to cause the same problems as any renin–angiotensin system inhibition strategy, including relevant decreases in renal function in patients with vascular disease and hyperkalemia. Contraindication in pregnancy or in women contemplating such a move is a given. Time and future studies will tell.

FOOD FOR THOUGHT

Robert Tigerstedt and Bergman[30] would be bemused to see where their initial discovery of renin has led. The renin–angiotensin system has been a never-ending story with many new beginnings. One story warranting more discussion here concerns prorenin and the prorenin/renin receptor that were briefly mentioned earlier. Luetscher and co-workers[31,32] published two remarkable papers 20 years ago showing that diabetic target organ complications correlate not with PRA but rather with prorenin, a proenzyme that at that time had no known additional biological function or activity. Since then, we have learned that diabetics, in particular, appear to benefit from renin–angiotensin system blockade, even though their PRA values are low rather than high. Interestingly, prorenin is also made in the eye, a particularly important diabetic target organ.[33] The prorenin/renin receptor may be important here (Figure 2).[34,35] The receptor activates prorenin locally at the tissue level. No evidence has been shown that aliskiren blocks the interaction between prorenin and the prorenin/renin renin receptor. However, aliskiren would be anticipated to be very effective in preventing activated prorenin from cleaving angiotensinogen to generate Ang I locally. The 'tissue renin–angiotensin system,' as we currently understand it, would be expected to be blocked by such an effect. The prorenin/renin receptor is activated with equal facility by both renin and prorenin.

Although aliskiren lowers PRA, the concentration of the enzyme renin, as Oparil *et al.*[26] have observed, increases to high levels. High renin concentrations could conceivably interact with the prorenin/renin receptor. This activation could initiate ERK1/2 signaling, transforming growth factor-beta (TGF-β) activation, and other potentially serious consequences. Sealey and Laragh[10] alluded to this possibility, although they presented no data to this issue. Deleterious effects signaled by the prorenin/renin receptor have not been observed in animal models and neither have they been described in patients. Nevertheless, Ichihara and co-workers[35,36] have published an exciting series of papers suggesting that prorenin could raise havoc independent of Ang II generation by signaling via the prorenin/renin receptor (Figures 2 and 3). Ichihara and co-workers[37–42] have produced a decoy protein that blocks the development of diabetic nephropathy and eye changes in models independent of Ang II generation. As a matter of fact, their models include AT1 receptor gene-deleted mice that cannot signal via the AT1 receptor. These findings are provocative and controversial and indicate that much more work needs to be done.[43] However, such signaling would not be amenable to ACE inhibitor, ARB, or direct renin inhibitor (aliskiren) therapy. Whether or not the future is bright remains to be seen. Nonetheless, it is certain to not be dull!

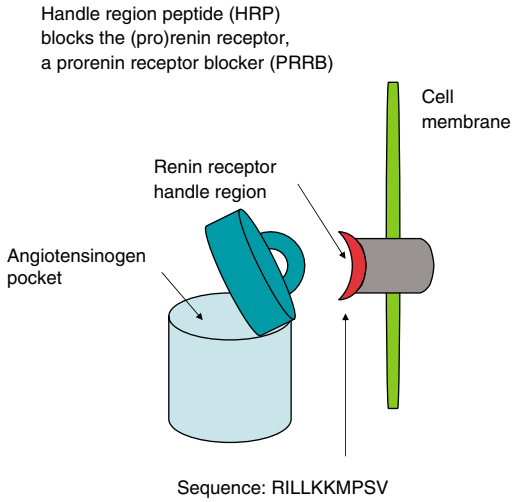

Figure 3 | A decoy peptide sequence (handle region peptide) has been developed that may block prorenin signaling at the renin receptor.

DISCLOSURE

Friedrich C Luft is an advisor to Novartis Inc. and has received grants in aid to study aliskiren in animal models. He has also spoken on aliskiren at national and international meetings in the framework of Renin Academy programs. Myron H Weinberger has been an investigator in studies of aliskiren in hypertensive patients. He has also lectured on aliskiren.

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